

## REMARKS

### *The Present Invention and the Pending Claims*

The present invention pertains to a high-throughput method of distinguishing at least one molecule individually in a sample comprising multiple molecules, comprising imaging and determining the electrophoretic mobility of the molecule to be detected. Claims 1-23 and 57-91 are currently pending.

### *Summary of the Office Action*

Claims 7 and 71 have been rejected under 35 U.S.C. § 112, second paragraph, as indefinite.

Claims 1, 3-8, 11-13, 15-18, 21, 22, 58, 60-62, 65, 67-72, 74-76, 78-80, 83, 84, 86, 88, and 89 have been rejected under 35 U.S.C. § 102(e), as allegedly anticipated by U.S. Patent No. 6,485,625 (Simpson et al.).

Claims 9, 10, and 73 stand rejected under 35 U.S.C. § 103(a), as allegedly obvious in view of U.S. Patent No. 6,485,625 (Simpson et al.) in combination with U.S. Patent Nos. 6,221,592 (Schwartz et al.) and 5,215,883 (Chu).

Claims 14, 23, 57, 77, and 85 stand rejected under 35 U.S.C. § 103(a), as allegedly obvious in view of U.S. Patent No. 6,485,625 (Simpson et al.) in combination with U.S. Patent Nos. 6,586,193 (Yguerabide et al.) and 6,120,667 (Hayashizaki et al.).

Claims 19, 20, 63, 64, 81, 82, 90, and 91 stand rejected under 35 U.S.C. § 103(a), as allegedly obvious in view of U.S. Patent No. 6,485,625 (Simpson et al.).

Claims 59 and 87 stand rejected under 35 U.S.C. § 103(a), as allegedly obvious in view U.S. Patent No. 6,485,625 (Simpson et al.) in combination with U.S. Patent No. 5,538,613 (Brumley et al.).

Claims 2 and 66 stand objected to as being dependent upon a rejected base claim.

These rejections are respectfully traversed and reconsideration of the pending claims is respectfully requested in view of the following remarks.

### *Discussion of the Section 112, second paragraph, Rejection*

According to the Examiner, the term "small molecule" in claims 7 and 71 is indefinite because it is a relative term that is not defined by the claim. Applicants submit that the term

“small molecule” is considered well known in the art, in particular, biological-related arts. In particular, a “small molecule” is any molecule that is not considered a macromolecule, which includes a protein, a nucleic acid, a carbohydrate, or a lipid. The specification at page 12, lines 15-25 points out to one skilled in the art what applicant meant by “small molecules.” Thus, examples of a “small molecule” include a drug, coenzyme (e.g., a vitamin), or a ligand (e.g., an antigen, a hormone, or neurotransmitter). The present application provides an example of a “small molecule.” In Example 2, digoxin, a drug for the treatment of heart failure, is disclosed (see, for example, paragraph [0121]). Therefore, since the term “small molecule” is a term well understood in the art, claims 7 and 71 are considered definite.

*Discussion of the Anticipation and Obviousness Rejections*

Claims 1, 3-23, 57-65, and 67-91 have been rejected as allegedly either anticipated or obvious in view of the cited references.

*A. The Anticipation Rejection*

Claims 1, 3-8, 11-13, 15-18, 21, 22, 58, 60-62, 65, 67-72, 74-76, 78-80, 83, 84, 86, 88, and 89 stand rejected as anticipated by Simpson et al. The Office contends that Simpson et al. discloses the inventive method of independent claims 1 and 65. This rejection is traversed for the reasons set forth below.

The present invention, as defined by claim 1, is directed to a high-throughput method of distinguishing *at least one* molecule individually in a sample comprising multiple molecules, which method comprises:

(i) subjecting a sample comprising multiple molecules, at least one molecule of which is detectably labeled, to electrophoresis,

(ii) imaging the electrophoretic mobility of each detectably labeled molecule over time by detecting the position of the detectable label of each detectably labeled molecule over time and, optionally, at the same time, dispersing the imaging by a transmission grating for spectroscopic analysis, and

(iii) determining the electrophoretic mobility of each detectably labeled molecule and, optionally, determining the molecular spectrum of each detectably labeled molecule, thereby distinguishing *at least one* molecule individually in a sample comprising multiple molecules.

Claim 65 is directed to a high-throughput method of distinguishing *at least one* molecule individually in a sample comprising multiple molecules, which method comprises:

- (i) introducing a sample comprising multiple molecules in free solution, at least one molecule of which is detectably labeled, into a sample channel,
- (ii) simultaneously imaging the position of each detectably labeled molecule by detecting the position of the detectable label of each detectably labeled molecule and dispersing the imaging by a transmission grating for spectroscopic analysis, and
- (iii) determining the molecular spectrum of each detectably labeled molecule, thereby distinguishing *at least one* molecule individually in a sample comprising multiple molecules.

The presently claimed methods require distinguishing at least one molecule individually in a sample comprising multiple molecules. In contrast, Simpson et al. discloses a method for the detection of molecules in a sample, which method requires amplification in order to obtain enough sample to provide a spectroscopic signal (see col. 6, lines 35-42 and col. 29, line 24, through col. 30, line 17 of Simpson et al.). Amplification is required to provide hundreds of thousands of copies of a molecule of interest. Thus, Simpson et al. describes the detection of many molecules of one type at a time. Moreover, Simpson et al. does not disclose a method that can distinguish *one molecule* individually in a sample comprising multiple molecules, as presently claimed. Nothing in Simpson et al. teaches or suggests the individual detection of a *single molecule*. Accordingly, the methods of claim 1 and 65 are completely different from the method described in Simpson et al. Each of claims 1, 3-8, 11-13, 15-18, 21, 22, 58, 60-62, 65, 67-72, 74-76, 78-80, 83, 84, 86, 88, and 89 includes an element not taught by Simpson et al. Therefore, each of these claims is novel over Simpson et al. Thus, the Section 102 rejection should be withdrawn.

#### *B. The Obviousness Rejections*

Claims 9, 10, 14, 19, 20, 23, 57, 59, 63, 64, 73, 77, 81, 82, 85, 87, 90, and 91 stand rejected as allegedly obvious over Simpson et al. in view of Schwartz et al., Chu, Yguerabide et al., Hayashizaki et al., and/or Brumley et al. The Office cites the secondary references for their disclosure of photobleaching, a pinhole, equilateral prism, acquisition rates, and a microscope objective. The rejection contends it would have been obvious to combine the method of Simpson et al. with the disclosures of Schwartz et al., Chu, Yguerabide et al., Hayashizaki et al., and/or Brumley et al. in order to optimize the detection system. This rejection is traversed for the reasons set forth below.

In re Appln. of Yeung et al.  
Application No. 10/031,353

As described above, Simpson et al. does not disclose all of the elements the present invention. In particular, Simpson et al. does not teach or suggest a method of distinguishing *at least one molecule* individually in a sample comprising multiple molecules. Further, Schwartz et al., Chu, Yguerabide et al., Hayashizaki et al., and/or Brumley et al. do not fill the gap between the claimed invention and Simpson et al. Schwartz et al., Chu, Yguerabide et al., Hayashizaki et al., and/or Brumley et al. disclose only a single element (e.g., photobleaching), and not the overall detection method. Nothing in any of these cited secondary references teaches the individual detection of a single molecule. Further, none of the references suggests that Simpson et al. could be modified so that the method of Simpson et al. would be capable of distinguishing *at least one* detectably labeled molecule individually as in the claimed method. Thus, the combinations of the disclosures of Simpson et al. and the cited secondary references do not result in the present invention of claims 9, 10, 14, 19, 20, 23, 57, 59, 63, 64, 73, 77, 81, 82, 85, 87, 90, and 91. Accordingly, since none of the cited references, alone or in the alleged combinations suggested by the Office, renders the method of claims 9, 10, 14, 19, 20, 23, 57, 59, 63, 64, 73, 77, 81, 82, 85, 87, 90, and 91 obvious, the obviousness rejections should be withdrawn.

In view of the foregoing, all of the pending claims are patentable over the cited references. Applicants request that the rejections be withdrawn.

#### *Conclusion*

The application is considered in good and proper form for allowance, and the Examiner is respectfully requested to pass this application to issue. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,



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Date: March 30, 2004